UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

August 18, 2016

MEMORANDUM

SUBJECT: Dodecylguanidine hydrochloride (DGH): Human Health Scoping Document in Support of Registration Review.

PC Code: 044303	DP Barcode: D434922
Decision No.: 519801	Registration No.: N/A
Petition No.: N/A	Regulatory Action: Reg Review Scoping
Risk Assess Type: Single Chemical	Case No.: 0161
TXR No.: N/A	CAS No.: 13590-97-1
MRID No.: N/A	40 CFR: N/A

FROM: Timothy Dole, CIH, Industrial Hygienist
Timothy McMahon, Ph.D., Toxicologist
Julie Van Alstine, MPH, Environmental Health Scientist
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (AD)

THROUGH: Timothy Leighton, Senior Scientist
Steven Weiss, Branch Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (AD)

TO: Wilhelmena Livingston, Chemical Review Manager
Kevin Costello, Branch Chief
Risk Management and Implementation Branch IV
Pesticide Re-evaluation Division

AND

Stephen Savage, Chemical Review Manager
Rose Kyprianou, Acting Branch Chief
Regulatory Management Branch II
Antimicrobials Division

Attached is the Agency's human health risk assessment scoping document for DGH's antimicrobial uses submitted in support of Registration Review.

1 Introduction

Dodecylguanidine hydrochloride (DGH, PC 044303) is 1 of 3 active ingredients (ai's) included in registration review Case #0161. The other two ai's include dodecylguanidine acetate (dodine, PC 044301) and dodecylguanidine terephthalate (DGT, PC 044302). DGH has only antimicrobial registrations, dodine has only conventional registrations, and DGT has no registrations. A separate document has been written by the Health Effects Division (HED) to outline the risks and data gaps for dodine (Peter Savoia, August 25, 2016, D427768).

To evaluate the scope of work necessary to support Registration Review for DGH, AD has considered recent risk assessments for Dodine/DGH, the Human Health Risk Assessment for the 2006 Registration Eligibility Document (RED), updates to its toxicity, exposure and usage databases, and the latest Agency science policy and risk assessment methodologies. The most recent risk assessment for DGH was conducted in 2005 as an addendum to the dodine RED (Cassi Walls, June 21, 2005, D313682 and 313684).

1.1 FFDCA Clearances

EPA has not established tolerances for residues of DGH; however, DGH is closely related to dodine, an agricultural pesticide that belongs to the guanidine class of fungicides and is commonly used as a foliar protectant against various diseases of fruits and nuts. Tolerances are established for residues of dodine and its metabolites in various raw agricultural commodities in 40 CFR §180.172. There are no tolerance exemptions for residues of DGH under the Federal Food, Drug, and Cosmetic Act (FFDCA) Section 408. DGH has been cleared as an indirect food additive by the US Food and Drug Administration (US FDA) under FFDCA Section 409 as a component of paper and paperboard in contact with aqueous and fatty foods (21 CFR §176.170) and as a slimicide (21 CFR §176.300). There are no food contact notifications for DGH.

- 21 CFR §176.170: DGH is cleared for use only as an antimicrobial agent in paper and paperboard under the following conditions: 1) for contact only with nonalcoholic food having a pH above 5 and provided it is used at a level not to exceed 0.4% by weight of the paper and paperboard; and 2) for use in the outer ply of multiwall paper bags for contact with dry food of Type VIII described in table I of paragraph (c) of this section and provided it is used at a level of 0.8% by weight of the paper. The Agency notes that a similar clearance is established for dodine. The DGH paper and paperboard assessments are considered to be protective of the established US FDA dodine clearance for paper and paperboard (21 CFR §176.170).
- 21 CFR §176.300: DGH is cleared at a maximum level of 0.20 pound per ton of dry weight fiber.

1.2 Use Information

Currently there are 14 total FIFRA Section 3 registrations for DGH. DGH is manufactured as a 35% technical material or formulation intermediate (3 registrations) and is formulated into end

use antimicrobial products (11 registrations) that contain 5 to 35% ai. All of the end use products are liquid formulations.

DGH is registered for use in industrial processes and water systems (IPWS), as a material preservative and as wood preservative for sapstain control. Some of the materials preservation uses result in indirect dietary exposures to DGH. DGH is also regulated under 21CFR 176.300 as a slimicide for controlling bacteria, yeasts, and fungi that can cause deterioration of paper and paperboard products. A listing of the uses and application rates is included in Table 1.

Table 1 - DGH Uses and Application Rates

Use	Application Rate	Application Rate Units
Industrial Processes and Water Systems		
Air Washer Systems	9 to 35	ppm ai
Brewery Pasteurizer Water	15 to 35	ppm ai
Cooling Water Systems, Once Through	3 to 6	ppm ai
Cooling Water Systems, Recirculating	9 to 35	ppm ai
Oil Drilling and Recovery Fluids, Muds and Water Systems	15 to 35	ppm ai
Oil Process Waters	300	ppm ai
Pulp and Paper Water Systems	12 to 53	ppm ai
Sewage Disposal Lagoons	8.2 to 14.2	lb ai/acre
Wastewater Systems	12 to 24	ppm ai
Material Preservation		
Adhesives, glues and automobile adhesive tapes	350	ppm ai
Caulks and Sealants	1500	ppm ai
Food Packaging Multiwall Paper Bags for Dry Food (outer ply only)	8000	ppm ai
Food Packaging Paper and Paperboard (direct contact)	4000	ppm ai
Leather[1]	10500	ppm ai
Metal Working Fluids[1]	1500 to 7200	ppm ai
Paints, Coatings and Stains	350 to 1060	ppm ai
Paper and Paperboard for Industrial/Agricultural Use	8000	ppm ai
Paper Chemicals, Adhesives and Coatings	30 to 350	ppm ai
Pastes (wallpaper paste, wood glue, non-food packaging adhesives)	350 to 1500	ppm ai
Pigments, Dyes and Fillers	350 to 1500	ppm ai
Polymer Dispersions and Emulsions	350 to 1500	ppm ai
Textiles[1]	10500	ppm ai
Wood Preservation		
Sapstain Control - Construction Woods, Fresh Cut Lumber, Pallets[1]	21000	ppm ai
Sapstain Control - Fruit and Vegetable Containers[1]	15000	ppm ai

[1] Only one label (39967-116, transferred from 67869-44) has this use.

2 Incident Report

As of (6/8/2016), there is one incident for DGH in the OPP Incident Database System. This incident occurred in 1998 and was rated as minor severity.

3 Toxicology Hazard Characterization and Endpoint Selection

3.1 Absorption, Distribution, Metabolism, and Excretion (ADME)

In an acceptable ADME study (MRID 42479001), dodine was administered orally to male and female Sprague-Dawley rats at single doses of 40 or 400 mg/kg radiolabeled dodine, or as a repeated oral dose of non-radiolabeled dodine at 40 mg/kg/day for 14 days, followed by a single radiolabeled dose of dodine at 40 mg/kg. Intravenous dosing was not possible with dodine due to its insolubility in vehicles suitable for intravenous administration. Urine and feces were found to be major routes of excretion. At 120 hours (5 days) post-exposure, 41-45% of the dose was excreted in the urine and 48-60% was excreted in the feces in all dose groups. Total recovery at 120 hours ranged from 94-102% of the administered dose. Less than or equal to 3% of the administered dose was recovered in tissues. The highest amounts recovered were in the gastrointestinal tract (0.16-1.14% of the dose), muscle (0.02-0.61% of the dose) and skin (0.06-0.21%). Biliary cannulation was not performed, and it is not clear if the presence of the parent compound in the feces was the result of poor intestinal absorption or due to biliary excretion.

The proposed metabolic pathway for dodine in rats is a ß-oxidation pathway similar to that for medium- and long-chain fatty acids. Dodine is activated in the liver by formation of a CoA derivative. This then enters the mitochondria where β-oxidation takes place. Oxidation produces intermediate products with shorter chain lengths which are eliminated in the urine. Urea is also formed in the liver from action on dodine or one of its metabolites.

3.2 Dermal Absorption

A dermal penetration study (MRID 46621303) is available for dodine in which [^{14}C] - Dodine (n-dodecyl-^{14}C guanidine acetate) was administered (single topical application for 8 hours) to three groups of four male Sprague Dawley CD rats/dose to a 12 cm^2 dorsal area in a formulation and water dilution; doses were 4.0 and 0.004 mg/ cm^2. The absorption and excretion of radiolabeled material was determined at 8, 24, 48 and 72 hours following the single topical application of radioactive dodine. The mean percent radioactivity remaining in the treated skin in the 0.004 mg/cm^2 groups were 36.6%, 49.5%, 45.2% and 40.3% at 8, 24, 48, and 72 hours, respectively. The radioactivity remaining at the application site increased slightly over time. The percentage of radioactive material absorbed (the urine, feces, cage wash, carcass and untreated skin) remained fairly constant (0.59% to 0.77%). Therefore, approximately 1% (0.77%) of the dose applied to male rats was demonstrated to be absorbed through skin at the 0.004 mg/cm^2 dose (low dose) at the 72 hour time point.

The Agency considers dodine and DGH toxicologically equivalent. The toxicology database for dodine/DGH is incomplete for evaluating and characterizing toxicity and selecting endpoints for risk assessment. The HED Hazard and Science Policy Council (HASPOC) recommended in 2013 that the subchronic inhalation toxicity study not be waived for dodine/DGH, based on the irritating properties of dodine by the inhalation route, and unacceptable estimated margins of exposure from the use of an oral endpoint for inhalation risk assessment (February 8, 2013; TXR

0056498). Acute and subchronic neurotoxicity studies are also not available; however, HASPOC recommended that these studies be waived for dodine, based on the low acute toxicity of dodine, the lack of evidence for neurotoxicity in the dodine toxicology database, and lack of evidence of neurotoxicity for structurally-related chemicals (February 8, 2013; TXR 0056498). The requirement for a subchronic (28-day) inhalation toxicity study (OCSPP 870.3465) was re-affirmed by HASPOC in July of 2016 (TXR 0057429). Toxicological endpoints for dodine/DGH were selected by the HED Toxicology Science Advisory Council (ToxSAC) in March of 2016. It is anticipated that the inhalation points of departure and uncertainty factors will likely be modified once the inhalation toxicity study is submitted and reviewed. Below is a summary of the available toxicology studies for Dodine and DGH.

3.3 Toxicological Effects of Dodine and DGH

3.3.1 Dodine

A definitive target organ was not identified for dodine in the available toxicology data. The most common effects observed in subchronic and chronic studies in rats and dogs were decreases in food consumption, body weight and/or body weight gain. LOAELs/NOAELs were not updated to indicate that body weight gain change per se is not an adverse effect, and thus LOAELs based on this effect are protective of systemic toxicity. When allometric scaling ($BW^{3/4}$) is used to adjust to a human equivalent dosage, the dog was found to be the most sensitive species for this endpoint (Table 4.3.1). There was no evidence of progression of toxicity with time. There was also no indication that the observed toxic effects were a consequence of unpalatability of the food. There was also no evidence of neurotoxicity.

In a rat 28-day dermal toxicity study, no systemic toxicity was noted; histopathological alterations were limited to dermal lesions.

Decreased maternal body weight gain and food consumption were the only effects observed in a rat developmental toxicity study. In a rabbit developmental toxicity study, does demonstrated decreased food consumption. No treatment-related effects were observed in fetuses in the developmental studies in rats or rabbits. There was no evidence of increased susceptibility to fetuses in these studies.

Dodine did not adversely affect reproductive parameters in rats over two generations. However, at the highest dose of 53 mg/kg/day, decreases in parental body weight, body weight gain and food consumption were noted in both generations of rats. Furthermore, the offspring of both generations demonstrated decreased body weight after post-natal day 4 which continued through pre-mating. There was no evidence of increased susceptibility to offspring in this study. Offspring effects (decreased pup weight) were observed in the presence of comparable maternal effects (decreased body weight).

3.3.2 DGH

The toxicology database for DGH is limited in comparison to dodine; however, based on previous Agency determinations, the dodine toxicology database can be used for addressing hazard of DGH. The Agency determined that the two chemicals are toxicologically equivalent, based on the following: the cationic species from both dodine and DGH is identical; the NOAEL/LOAEL values for both dodine and DGH are similar when comparing similar studies; the adverse effects of both chemicals are also the same, and the acute toxicity profiles (Toxicity Categories) for dodine and DGH are the same.

Similar to study results observed with dodine, the toxicology study data on DGH do not identify a definitive target organ but show similar effects after administration (decreased body weight and/or weight gain, decreased food consumption, and salivation). There is no evidence for developmental toxicity for both dodine and DGH. Dodine and DGH are also both negative for mutagenicity. In the developmental toxicity study in rats with DGH, excessive salivation and moist rales were observed in maternal animals. This could be based on the irritancy of the test chemical. There was no developmental toxicity observed at any dose level in this study.

In the 90-day oral toxicity study in dogs, excessive salivation, emesis, and thin/emaciated appearance were observed in dogs at 35 mg/kg/day. In the 21-day dermal toxicity study, there were no systemic effects observed. Dermal irritation, including erythema, desquamation, fissuring, and edema, was observed at all doses tested.

Results of mutagenicity testing of DGH showed it to be negative for induction of erythrocyte micronuclei and for induction of unscheduled DNA synthesis in rat hepatocytes.

3.4 Safety Factor for Infants and Children (FQPA Safety Factor)[1]

There is no evidence of susceptibility following *in utero* and/or postnatal exposure in the developmental toxicity studies in rats or rabbits, and in the 2-generation rat reproduction study. The Agency reduced the FQPA safety factor to 1x for all exposure scenarios. For inhalation exposures, the Agency retained a 10X database uncertainty factor (UF_{DB}) to account for the lack of an acceptable inhalation toxicity study in the rat.

3.4.1 Completeness of the Toxicology Database

The toxicology database for dodine is complete with respect to assessing potential risk to infants and children and females 13-49 years of age. The database for assessing potential risk to these subpopulations contains the following toxicity studies: prenatal developmental studies (rat and rabbit); and a reproduction study in rats.

[1] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

3.4.2 Evidence of Neurotoxicity

Neurotoxicity studies are not available for dodine or DGH. Clinical signs (excessive salivation and hunched posture/hypoactivity) were observed in chronic studies of dodine in rats and mice but were not dose-related or statistically significant. Excessive salivation in dogs after dodine (capsule) exposure showed a treatment-related dose response; however, it was not consistent with a neurological adverse effect since it was seen prior to dosing and was a persistent finding throughout the study. It is possible that the excessive salivation was a result of the irritant properties of dodine. In addition, no evidence of neuropathology was observed in the available studies. HASPOC recommended waiving the requirement for the acute and subchronic neurotoxicity studies, based on (1) the low acute oral toxicity of dodine (Toxicity Category III); (2) the lack of neurotoxicity in the dodine toxicity database; and (3) no neurotoxicity concerns for structurally related compounds to dodine (February 8, 2013; TXR 0056498).

3.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Based on the available dodine/DGH toxicity studies, there was no evidence of increased susceptibility (quantitative or qualitative) in pups or fetuses versus adults based on rat and rabbit developmental studies and the rat multi-generation reproduction study. In rat and rabbit prenatal developmental studies, there was no toxicity identified in the fetuses up to the highest dose tested. In the two generation reproduction study, decreases in body weight and food consumption were seen in pups at the same dose at which maternal toxicity (decreased body weight, body weight gain and food consumption) was observed.

3.5 Toxicological Endpoints for dodine/DGH

The current endpoints for dodine/DGH are shown below. The endpoints for dietary and incidental oral exposure are the same as those included in the HED scoping and risk Assessment document for dodine (Peter Savoia, August 25, 2016, D427768). The Agency anticipates the need to revise the dermal and inhalation human health risk assessment for DGH based on (1) the updated toxicology endpoints shown in Table 2 including an endpoint for dermal irritation that was not in the dodine risk assessment, and (2) the anticipated 28-day inhalation toxicity study (OCSPP 870.3465) that will result in a revision to the current inhalation endpoint.

Table 2 - Toxicological Points of Departure for DGH Human Health Risk Assessment

Exposure/ Scenario	Point of Departure (POD)	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	Not Applicable - No appropriate endpoint identified resulting from a single exposure.			
Acute Dietary (Females 13-49)	Not Applicable - No appropriate endpoint for females age 13-49 identified resulting from a single exposure.			
Chronic Dietary (All Populations)	NOAEL = 2 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Chronic RfD = 0.02 mg/kg/day cPAD = 0.02 mg/kg/day	Chronic toxicity – dog, MRID 44246101 LOAEL = 10 mg/kg/day based on marked body weight loss and food consumption in individual females.
Incidental Oral Short-Term (1-30 days) Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 8.75 mg/kg/day	UF_A=10X UF_H=10X FQPA = 1X	LOC =100	90-day oral toxicity study in dogs (DGH), MRID 41316903 LOAEL = 35 mg/kg/day, based on body weight decreases at the next highest dose of 35 mg/kg/day
Dermal **systemic,** Short- and Intermediate-Term	Not Applicable - No endpoint for systemic toxicity from dermal exposure was identified in the database for Dodine or DGH.			
Dermal **irritation** Short- and Intermediate-Term	NOAEL = 4.3 mg/kg/day (ai adjusted) (52 µg ai/cm^2)[1]	UF_A=10X UF_H=10X $FQPA_{DB}$ =1X	Occupational LOC = 100 Residential LOC = 100	21 -Day Dermal Toxicity Study (DGH), MRID 41316901 LOAEL = 8.75 mg/kg/day (ai adjusted), based on dermal irritation effects (edema, erythema, desquamation, fissuring)
Inhalation Short- and Intermediate-Term	NOAEL = 8.75 mg/kg/day	UF_A=10X UF_H=10X UF_{DB} =10X	Occupational LOC = 1000 Residential LOC = 1000	90-day oral toxicity study in dogs (DGH), MRID 41316903 LOAEL = 35 mg/kg/day, based on body weight decreases at the next highest dose of 35 mg/kg/day
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity			

UF = uncertainty factor, UF_{DB} =10X for lack of an inhalation toxicity study.

NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, LOC = level of concern

[1] The applied concentration at 4.3 mg/kg/day is 2.18 mg ai/ml and the dose volume is 2 ml/kg. The average (M +F) rat body weight is 300 grams thus the dose volume per rat is 0.60 ml. The dose is 2.18 mg ai/ml x 0.60ml = 1.3 mg ai and the applied area is 25 cm^2. The surface loading is 1.3 mg/ai/25 cm^2 which equals **52 µg ai/cm^2**

3.6 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for dodine, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), dodine is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[2] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

[2] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[3] http://www.epa.gov/endo/

4 Residue Chemistry and Dietary Exposure

Screening-level chronic dietary exposure assessments have been conducted using current assumptions to estimate indirect dietary exposure due to use of DGH as a slimicide in the manufacture of paper and paper products, and as a paper food-packaging, adhesive, polymer, and lumber materials preservative. The most recent dietary exposure assessment for DGH was conducted in 2005 for the registered DGH slimicide, paper coating, and paper adhesive uses (Memo, C. Walls; 21-JUN-2005). The Agency notes that the following paper migration studies have been submitted: MRIDs 46602701, 46602702, and 46602703. The Agency will review these studies as part of Registration Review. Revised dietary assessments may be conducted as part of Registration Review that reflect updates to toxicology data and the submission of paper, polymer, and lumber migration data to refine the dietary assessments. Additionally, US FDA clearances and/or food contact notifications for uses of DGH in adhesives (EPA Reg. No. 39967-115), polymers (EPA Reg. No. 39967-115), and on lumber used to build fruit and vegetable containers (EPA Reg. No. 39967-116) are required.

4.1 Total Estimated Daily Dietary Intake (TEDDI) Assessment

In addition to estimating direct and indirect antimicrobial dietary exposures and risks, AD also completes an assessment to determine if the total estimated daily dietary intake (TEDDI) of an antimicrobial for all population subgroups is above or below 200 ppb. In general, if this assessment indicates that the TEDDI is greater than 200 ppb for any of the assessed population subgroups, additional (Tier II) toxicity data are required as listed in 40CFR §158.2230(d). The dodine/DGH toxicity database is complete at this time; therefore, a TEDDI assessment was not conducted for DGH.

4.2 Paper and Paperboard Components

DGH is cleared for use as a component of paper and paperboard in contact with aqueous and fatty foods by the US FDA. It can be used at rates up to 0.4% by weight of the paper and paperboard for nonalcoholic food having a pH above 5 and up to 0.8% by weight of the paper for use in the outer ply of multiwall paper bags for contact with dry food. (See 21 CFR §176.170 for additional details.) The following labels include paper and paperboard component uses that are at the US FDA clearance rates of 0.4% and/or 0.8% by weight: EPA Reg. Nos. 39967-107; 39967-115; 39967-116; 39967-123; 39967-126; 74655-12; and 74655-7.

Screening-level chronic dietary assessments were conducted with the Slimicides Model using the paper and paperboard application rates of 0.4% by weight (4000 ppm ai) and 0.8% by weight (8000 ppm ai) of the paper and paperboard. Both assessments used 2003-2008 NHANES/WWEIA consumption data; however, the 0.4% by weight assessment used total (liquid and solid) grams of food consumed and the 0.8% by weight assessment used grams of solid food consumed based on the US FDA clearance the label restrictions that indicate that the product is for use in the manufacture of the outermost ply of multiwall paper bags intended for use as containers for dry food (i.e., dry solids with the surface containing no free fat or oil) (EPA

Reg. Nos. 39967-123 and 39967-126 only). Both assessments assumed that 20% of food consumed in the human diet may contact paper and that 100% of residues in paper migrate into food. Both the 0.4% by weight and 0.8% by weight assessment resulted in risks of concern for the general US population and all population subgroups (Tables 3 and 4). These assessments could be refined using migration data, as discussed in the Data Requirements section, below.

EPA notes that in addition to the clearance rates, some labels also included paper material preservation uses at rates that are below the clearance level (≤ 50 ppm ai; EPA Reg. Nos. 39967-107; 39967-115; 39967-116; 74655-12; 74655-7). No dietary risk estimates of concern were found at these lower use rates.

Table 3 - Chronic Exposure Assessment for Use of DGH as a Paper and Paperboard Component at 0.4% by Weight.

Population Subgroup	BW (kg)	Total Food Consumed (g)	DC (µg ai/g food)	EDI (µg ai/ person/day)	DDD (mg ai/ kg bw/day)	% cPAD
General U.S. Population	70.2	3910	4	15640	0.223	1100
All Infants (<1 year old)	7.7	766		3064	0.398	2000
Children 1-2 years old	12.6	1770		7080	0.562	**2800**
Children 3-5 years old	18.7	1940		7760	0.415	2100
Children 6-12 years old	37.1	2460		9840	0.265	1300
Youth 13-19 years old	67.3	3050		12200	0.181	910
Adults 20-49 years old	81.5	4110		16440	0.202	1000
Adults 50-99 years old	81.2	3780		15120	0.186	930
Females 13-49 years old	72.9	3680		14720	0.202	1000

BW = Bodyweight; Mean weights from NHANES WWEIA 2003-2008
DC = Dietary concentration based on the Slimicide Model and EPA Reg. Nos. 39967-107; 39967-115; 39967-116; 39967-123; and 39967-126
EDI = Estimated daily intake = DC*Total Food Consumed
DDD = Daily dietary dose = (EDI*1 mg/1000 µg)/BW
%cPAD = % chronic Population-Adjusted Dose = (DDD/cPAD)*100%

Table 4 - Chronic Exposure Assessment for Use of DGH in Multiwall Paper Bags at 0.8% by Weight.

Population Subgroup	BW (kg)	Solid Food Consumed (g)	DC (µg ai/g food)	EDI (µg ai/person/day)	DDD (mg ai/ kg bw/day)	% cPAD
General U.S. Population	70.2	1510	8	12080	0.172	860
All Infants (<1 year old)	7.7	302		2416	0.314	1600
Children 1-2 years old	12.6	1150		9200	0.730	**3700**
Children 3-5 years old	18.7	1140		9120	0.488	2400
Children 6-12 years old	37.1	1280		10240	0.276	1400
Youth 13-19 years old	67.3	1220		9760	0.145	730
Adults 20-49 years old	81.5	1250		10000	0.123	610
Adults 50-99 years old	81.2	1160		9280	0.114	570
Females 13-49 years old	72.9	1090		8720	0.120	600

BW = Bodyweight; Mean weights from NHANES WWEIA 2003-2008
DC = Dietary concentration based on the Slimicides Model and EPA Reg. Nos. 39967-123 and 39967-126
EDI = Estimated daily intake = DC*Solid Consumed (note that the clearance and labels indicate this use is for treating paper used for paper bags to hold dry foods only)
DDD = Daily dietary dose = (EDI*1 mg/1000 µg)/BW
%cPAD = % chronic Population-Adjusted Dose = (DDD/cPAD)*100%

4.3 Slimicides

DGH is cleared for use as a slimicide by the US FDA at a maximum level of 0.20 pounds per ton of dry weight fiber (21CFR §176.300). The following DGH labels include slimicide uses: EPA Reg. Nos. 39967-107, 39967-115, 74655-12, and 74655-7. EPA Reg. Nos. 74655-12 and 74655-7 include application rates for additive systems in the manufacture of paper and paper products in pounds of product per 1000 gallons, which appears to result in applications that are greater than the US FDA clearance rate. These labels should be revised to reflect the US FDA clearance rates. A screening-level chronic dietary slimicide assessment was conducted with the Slimicides Model using an application rate of 4 pounds product per 1000 gallons (10.6% ai; 480 ppm product; 51 ppm ai; EPA Reg. No. 74655-7). The assessment used a conservative assumption that the DGH concentration in the whitewater was 51 ppm, and additional label clarification may assist in refining the slimicide dietary exposure and risk assessment. The assessment used 2003-2008 NHANES/ WWEIA consumption data and assumed that the product was applied to the slurry water, 20% of food consumed in the human diet may contact paper, and that 100% of residues in paper migrate into food. The resulting exposure and risk estimates utilize 26% of the cPAD for the general U.S. population and 67% of the cPAD for children 1-2 years old, the most highly-exposed population subgroup (Table 5).

Table 5 - Chronic Exposure Assessment for Use of DGH as a Slimicide in the Manufacture of Paper and Paper Products (51 ppm ai)

Population Subgroup	BW (kg)	Total Food Consumed (g)	DC (µg ai/g food)	EDI (µg ai/ person/day)	DDD (mg ai/kg bw/day)	% cPAD
General U.S. Population	70.2	3910	0.0948	371	0.00528	26
All Infants (<1 year old)	7.7	766		72.7	0.00944	47
Children 1-2 years old	12.6	1770		168	0.01330	**67**
Children 3-5 years old	18.7	1940		184	0.00984	49
Children 6-12 years old	37.1	2460		233	0.00629	31
Youth 13-19 years old	67.3	3050		289	0.00430	21
Adults 20-49 years old	81.5	4110		390	0.00478	24
Adults 50-99 years old	81.2	3780		359	0.00442	22
Females 13-49 years old	72.9	3680		349	0.00479	24

BW = Bodyweight; Mean weights from NHANES WWEIA 2003-2008
DC = Dietary concentration based on the Slimicides Model and EPA Reg. No. 74655-7; 4 pounds per 1000 gallons added to the pulp and paper mill system (10.6% ai; 480 ppm product, 51 ppm ai)
EDI = Estimated daily intake = DC*Total Food Consumed
DDD = Daily dietary dose = (EDI*1 mg/1000 µg)/BW
%cPAD = % chronic Population-Adjusted Dose = (DDD/cPAD)*100%

EPA notes that exposure estimates at the US FDA clearance rate of 0.20 pounds ai per ton of dry weight fiber utilize <1% of the cPAD (0.000114226 mg/kg/day) for the general U.S. population and 1.4% of the cPAD (0.00028809 mg/kg/day) for children 1-2 years old, the most highly-exposed population subgroup.

4.4 Adhesives

US FDA clearances have not been established for uses of DGH as a materials preservative in food-contact adhesives. EPA Reg. No. 39967-115 includes a non-paper adhesive use that did not clearly indicate that it was a non-food use; therefore, AD has completed a dietary assessment for this use. The assessment used the Adhesives Model and assumed, based on FDA guidance, that a maximum of 7 ppb of pesticide residues are likely to migrate from food packaging materials into the food. The resulting exposure and risk estimates utilize 2% of the cPAD for the general U.S. population and 5% of the cPAD for children 1-2 years old, the most highly-exposed population subgroup (Table 6). A US FDA clearance should be obtained for this use, or the label should be updated to reflect that it is for non-food use adhesives.

Table 6 - Chronic Exposure Assessment for Use of DGH in Non-Paper Adhesives.

Population subgroup	BW (kg)	Total Food Consumed (g)	DC (µg ai/g food)[1]	EDI (µg ai/ person/day)	DDD(mg ai/ kg bw/day)	% cPAD
General U.S. Population	70.2	3,910	0.007	27.4	0.000390	1.9
All Infants (<1 year old)	7.7	766		5.36	0.000696	3.5
Children 1-2 years old	12.6	1,770		12.4	0.000983	**4.9**
Children 3-5 years old	18.7	1,940		13.6	0.000726	3.6
Children 6-12 years old	37.1	2,460		17.2	0.000464	2.3
Youth 13-19 years old	67.3	3,050		21.4	0.000317	1.6
Adults 20-49 years old	81.5	4,110		28.8	0.000353	1.8
Adults 50-99 years old	81.2	3,780		26.5	0.000326	1.8
Females 13-49 years old	72.9	3,680		25.8	0.000353	1.8

[1] Based on FDA guidance, assumes a maximum of 7 ppb of pesticide residues are likely to migrate from food packaging materials into the food.
BW = Bodyweight; Mean weights from NHANES WWEIA 2003-2008
DC = Dietary concentration based on the Adhesives Model and the application rate of 350 ppm ai for Adhesive Systems (Non-paper) from EPA Reg. No. 39967-115
EDI = Estimated daily intake = DC*Total Food Consumed
DDD = Daily dietary dose = (EDI*1 mg/1000 µg)/BW
%cPAD = % chronic Population-Adjusted Dose = (DDD/cPAD)*100%

4.5 Polymers

US FDA clearances have not been established for uses of DGH as a materials preservative in food-contact polymers. EPA Reg. No. 39967-115 (35% ai) includes a polymer use that did not clearly indicate that it was for use in only non-food polymers; therefore, AD has completed a polymer dietary assessment using the Commercial Tier 1A Model. The chronic food-only dietary assessment assumed an application rate of 350 ppm ai (0.1% of material), a surface area of 4000 cm^2, and that 100% of residues migrate into the food. The resulting exposure and risk estimates utilize 100% of the cPAD for the general U.S. population and 910% of the cPAD for all infants, the most highly-exposed population subgroup (Table 7). These risk estimates could be further refined through the submission of migration or polymer-specific data. A US FDA clearance should be obtained for this use, or the label should be revised to indicate that it is for non-food use polymers only.

Table 7 - Chronic Exposure Assessment for Use of DGH in Polymers Using the Commercial Tier 1A Model (350 ppm ai[2])

Population Group	Exposure[1]	Risk Estimates
	Exposure (Dose) (mg/kg/day)	% cPAD (Food Only)
General U.S. Population	0.0199	100
All Infants (<1 year old)	**0.182**	**910**
Children 1-2 years old	0.111	560
Children 3-5 years old	0.0749	370
Children 6-12 years old	0.0377	190
Youth 13-19 years old	0.0208	100
Adults 20-49 years old	0.0172	86
Adults 50-99 years old	0.0172	86
Females 13-49 years old	0.0192	96

[1] Active on Surface (mg/cm^2) x surface area (2000 cm^2) x fraction transferred (100%) ÷ BW (kg)

[2] Based on EPA Reg. No. 39967-115; Calculated using 0.1% material x 10,000 = 1000 ppm product. Product is 35% ai. 1000 ppm x 0.35 = 350 ppm.

4.6 Lumber for Fruit and Vegetable Containers

US FDA clearances have not been established for uses of DGH as a materials preservative in food-contact lumber. EPA Reg. No. 39967-116 (30% ai) includes a spray/dip use for the treatment of lumber used to construct fruit and vegetable containers; therefore, EPA has completed a dietary assessment for this use. The assessment used the Commercial Tier 1A Model and assumed an application rate of 15000 ppm ai (5% spray/dip solution of a product that is 30% ai), a surface area of 4000 cm^2, and that 100% of residues migrate into the food. The resulting exposure and risk estimates utilize 4300% of the cPAD for the general U.S. population and 39000% of the cPAD for all infants, the most highly-exposed population subgroup (Table 8). These risk estimates could be further refined through the submission of migration data or residue decline data. A US FDA clearance should be obtained for this use or the label should be revised to remove this use.

Table 8 - Chronic Exposure Assessment for Use of DGH on Lumber for Fruit and Vegetable Containers Using the Commercial Tier 1A Model (15,000 ppm ai[2])

Population Group	Exposure[1]	Risk Estimates
	Exposure (Dose) (mg/kg/day)	% cPAD (Food Only)
General U.S. Population	0.855	4300
All Infants (<1 year old)	7.79	39000
Children 1-2 years old	4.76	24000
Children 3-5 years old	3.21	16000
Children 6-12 years old	1.62	8100
Youth 13-19 years old	0.892	4500
Adults 20-49 years old	0.736	3700
Adults 50-99 years old	0.739	3700
Females 13-49 years old	0.823	4100

[1] Active on Surface (mg/cm^2) x surface area (4000 cm^2) x fraction transferred (100%) ÷ BW (kg)

[2] Based on EPA Reg. No. 39967-116; Calculated using 5% spray/dip solution x 10,000 = 50000 ppm product. Product is 30% ai. 50000 ppm x 0.30 = 15,000 ppm.

4.7 Dietary Data Requirements

The residue chemistry data requirements for antimicrobial pesticides in 40 CFR §158.2290 state that residue chemistry data are required for antimicrobial end-use products with uses that may result in residues in or on food. However, residue chemistry data are not required if no adverse effects (no toxicity endpoints) are associated with dietary exposure to the active ingredient or if theoretical (high-end) dietary exposure estimates combined with the applicable toxicity endpoint result in acute and chronic dietary risks that are below the Agency's levels of concern. With that, if risks of concern are identified using these high-end screening techniques, residue data will be required.

The dietary exposure assessments presented above for DGH result in dietary risks that are above the Agency's levels of concern. Therefore, additional residue chemistry data are required.

For chemicals that have well-understood fate properties, a nature of the residue on surfaces study will not be required at this time. In such cases, a tiered approach to refine dietary exposure and risk estimates will be used. The first tier consists of a potable water rinse (PWR) study, which is designed to measure the amount of residues remaining on hard non-porous surfaces that may contact food following a PWR. The use of a PWR is only appropriate if labels indicate that a PWR is required on surfaces before contacting food. In the case of porous surfaces such as paper products, a PWR is not practical and such a study should not be conducted. If estimates of exposure do not exceed Agency's risk level of concern using PWR data, no additional migration data are required. However, if estimates of exposure still exceed EPA's risk level of concern following incorporation of PWR data, or if PWR data are not practical as described above, a migration study will be required. A migration study measures the transfer of residues remaining on surfaces to food items. The Agency will use information from both the PWR and migration studies to refine its dietary exposure assessments, as appropriate.

In the case of DGH, the approach described above may be used in lieu of conducting a nature of the residue on surfaces study.

5 Occupational and Residential Exposure

The Agency anticipates the need to revise the occupational and residential assessments conducted in support of the 2005 RED since the Margins of Exposure (MOE)s were calculated using toxicological PODs and exposure data that have since been updated. In particular, it will be necessary to reassess the inhalation exposures using the POD from the inhalation toxicity study that is anticipated to be required. It will also be necessary to reassess the dermal exposures using a POD that accounts for dermal irritation. Uses of DGH that may result in occupational and residential handler and post-application exposures are included in Tables 9, 10 and 11.

5.1 Occupational Handler Exposure

Occupational handler exposure may occur from industrial process and water treatment, material preservation and sapstain treatment uses of DGH. EPA anticipates the need to revise the occupational handler assessment conducted in support of the 2005 RED and to assess some additional uses, such as metal working fluids and sapstain treatments, which were not assessed in the RED. The occupational handler scenarios to be assessed are presented in Table 9.

Table 9 - Occupational Handler Exposure Scenarios for DGH Antimicrobial Uses

Scenario	Exposure Routes	Duration
Sewage Lagoon Treatment Using a Boat Mounted Spray Rig	Dermal, Inhalation	Short and Intermediate Term
Open pour for industrial process and water systems treatment and material preservation	Dermal, Inhalation	Short and Intermediate Term
Machinist Exposure to Treated Metal Working Fluids	Dermal, Inhalation	Short, Intermediate, and Long Term
Brush/Roller and Airless Sprayer Application of Treated Paint	Dermal, Inhalation	Short, Intermediate, and Long Term
Sapstain Control – Spray or dip application	Dermal, Inhalation	Short, Intermediate, and Long Term

5.2 Residential Handler Exposure

Residential handler exposure may occur from the application of DGH preserved paints and stains. EPA anticipates the need to revise the residential handler assessment conducted in support of the 2005 RED to account for the revised PODs as discussed previously for occupational handlers. The exposure scenario that will be evaluated is listed in Table 10.

Table 3 - Residential Handler Exposure Scenarios for DGH

Scenario	Exposure Routes	Duration
Brush/Roller and Airless Sprayer Application of Treated Paints and Stains	Dermal, Inhalation	Short and intermediate Term

5.3 Residential Post Application Exposure

Residential post-application exposure may occur from DGH treated textiles that are used to manufacture household items such as blankets, towels, and apparel and DGH treated leather that is used to manufacture clothing. The exposure pathways include incidental oral exposure for children who chew on blankets, towels and clothing and dermal exposure for adults and children who wear treated clothing made from treated textiles and leather. These exposures were not assessed for the RED and will need to be assessed for registration review. The exposure scenarios that will be evaluated are listed in Table 11.

Table 4 - Residential Post-Application Exposure Scenarios for DGH

Exposed Population	Exposure Scenario	Exposure Routes	Duration
Children	Mouthing DGH treated textiles	Incidental Oral	Short and Intermediate Term
Children and Adults	Wearing DGH treated textiles	Dermal	Short and Intermediate Term
Children and Adults	Wearing DGH treated leather items	Dermal	Short and Intermediate Term

6 Aggregate Risk Assessment

In accordance with the Food Quality Protection Act (FQPA), aggregate pesticide exposures and risks from three major sources (food, drinking water, and residential exposure) must be considered. Dodine and DGH are both salts of the same chemical. They dissociate similarly and are considered toxicologically equivalent, as opposed to separate chemicals that share a common mechanism of toxicity. As such, EPA has recommended that the routes of exposure (with the exception of dermal irritation) be combined for risk assessment of dodine and DGH.

In the Dodine Reregistration Eligibility Decision document, short, intermediate, and long-term aggregate risk assessments were conducted combining food (direct + indirect), water, and residential exposures to dodine in the RED. No aggregate risk of concern was identified using the target MOE of 100, except for the diaper use, which has since been cancelled.

As a part of registration review, an updated aggregate risk assessment is anticipated, based on updated points of departure and uncertainty factors recently determined for DGH. This assessment is likely to include dietary and drinking water exposures from the antimicrobials use of DHG and dietary and drinking water exposures from the conventional uses of dodine. The residential uses of DGH may also be included in the aggregate assessment depending upon the effects observed in the inhalation toxicity study.

7 Cumulative Risk Assessment

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to dodine/DGH and any other substances and dodine/DGH does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that dodine/DGH has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides

8 Human Studies

The previous DGH risk assessments relied in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure 1.1 (PHED) Database, Outdoor Residential Exposure Task Force (ORETF) database, Agricultural Handler Exposure Task Force (AHETF) database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[4]. In addition, the new studies that are being performed by the Antimicrobial Exposure Assessment Task Force (AEATF) are being reviewed by the Human Studies Review Board (HSRB) as they are designed and completed. The recommendations made by the HSRB are being implemented to ensure that AEATF study participants are fully informed and protected as required by the "Protection of Human Subjects" regulation.

9 Risk Assessment Updates and Data Deficiencies

9.1 Risk Assessment Updates

The risk assessment updates that are anticipated to be needed are summarized below.

Toxicology

- The inhalation POD and UF for DGH will likely be revised based on submission of new inhalation toxicity data. This will result in an update to the inhalation assessment.
- The dermal assessment for DGH will be based on the irritation POD and thus the assessment will likely be revised to account for dermal irritation.

Dietary and Aggregate Risk:

- Updated dietary and aggregate risk assessments for DGH may be necessary based on the updated points of departure and results of the anticipated paper migration study.
- Updated dietary assessments for DGH may be necessary based on the need for US FDA clearances and/or food contact notifications for uses of DGH in adhesives (EPA Reg. No. 39967-115), polymers (EPA Reg. No. 39967-115), and on lumber used to build fruit and vegetable containers (EPA Reg. No. 39967-116) and the submission of polymer and lumber migration data.

[4] Available at: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Occupational/Residential Exposure**:**

- An updated occupational and residential handler risk assessment may be necessary to reflect significant changes to the scenario-specific surrogate handler-exposure data, and to incorporate any significant change in toxicological endpoints, PODs, and/or UFs.
- An updated residential post-application risk assessment may be necessary in order to incorporate the indoor surface residue data for textiles and leather that are anticipated to be required and to incorporate any significant change in toxicological endpoints, PODs, and/or UFs.

9.2 Data Deficiencies

The Agency plans to require the following data for the DGH risk assessment:

Toxicology

- A subchronic (28-day) inhalation study is required (OCSPP 870.3465)

Dietary

- A paper migration study is required. The Agency notes that the following paper migration studies have been submitted: MRIDs 46602701, 46602702, and 46602703. The Agency will review these studies as part of Registration Review. If these studies are found to be acceptable, the additional paper migration study requirement will be waived.
- A polymer migration study is required. Additionally, a food contact notification or food additive clearance should be obtained from US FDA for use of DGH in polymers that contact food. Alternatively, the label (EPA Reg. No. 39967-115) could be revised to indicate that food contact uses are not allowed.
- A food contact notification or food additive clearance should be obtained from US FDA for use of DGH in adhesives that contact food. Alternatively, the label (EPA Reg. No. 39967-115), could be revised to indicate that food contact uses are not allowed.
- A lumber migration study is required. Additionally, a food contact notification or food additive clearance should be obtained from US FDA for use of DGH in lumber that contacts food. Alternatively, the fruit and vegetable crate uses in the label (EPA Reg. No. 39967-116) could be removed.
- EPA Reg. Nos. 74655-12 and 74655-7 should be updated so that all slimicide use rates are clearly below the US FDA clearance rate of 0.20 pounds per ton of dry weight fiber.

Occupational and Residential Exposure

- Indoor Dermal (875.1200) and Inhalation (875.1400) Exposure Studies are required to assess dermal and inhalation exposures from: 1) Open pouring of liquids for industrial process and water systems treatment and material preservation, 2) Brush/Roller and Airless Sprayer Application of Treated Paint, 3) Machinist's use of treated MWF, 4) Sapstain Control Dip and Spray Application, 5) Sewage Lagoon Treatment.
- Indoor Surface Residue Studies (875.2300) are required to assess incidental oral and dermal exposures to textiles and dermal exposures to leather.

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